

Fat Embolism Syndrome

Gavin M. Joynt, Thomas ST Li, Joey KM Wai, Florence HY Yap

Abstract

The classical syndrome of fat embolism is characterized by the triad of respiratory failure, neurologic dysfunction and the presence of a petechial rash. Fat embolism syndrome (FES) occurs most commonly following orthopedic trauma, particularly fractures of the pelvis or long bones, however non-traumatic fat embolism has also been known to occur on rare occasions. Because no definitive consensus on diagnostic criteria exist, the accurate assessment of incidence, comparative research and outcome assessment is difficult. A reasonable estimate of incidence in patients after long bone or pelvic fractures appears to be about 3-5%. The FES therefore remains an important cause of morbidity and mortality and warrants further investigation and research to allow proper

recognition as well as the development of preventive and therapeutic strategies. Early fracture fixation is likely to reduce the incidence of fat embolism syndrome and pulmonary complications; however the best fixation technique remains controversial. The use of prophylactic corticosteroids may be considered to reduce the incidence of FES and in selected high-risk trauma patients but effects on outcome are not proved. New reaming and venting techniques have potential to reduce the incidence of FES during arthroplasty. Unfortunately, no specific therapies have been proven to be of benefit in FES and treatment remains supportive with priority being given to the maintenance of adequate oxygenation.

Key words: respiratory failure, petechiae, rash, trauma, orthopedic, fracture

Introduction

The classical syndrome of fat embolism is characterized by the triad of respiratory failure, neurologic dysfunction and the presence of a petechial rash [1,2]. Fat embolism syndrome (FES) occurs most commonly

following orthopedic trauma, particularly fractures of the pelvis or long bones, however non-traumatic fat embolism is also known to occur [3-8]. The classical clinical triad of FES is not always present, and therefore diagnosis may be difficult and the reported incidence is variable. For example, in two studies evaluating similar cohorts of patients with major lower limb fractures, the reported incidence of the syndrome varied from 11% in the prospective study [3], to approximately 1% in the 10-year retrospective study [9]. Attributable mortality is also difficult to quantify and has previously been estimated to be about 10-20% [10], however with modern approaches to prevention and organ support therapy this is now likely to be much lower.

Much is still unclear about fat embolism some 150 years

From Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong (Drs. Gavin M. Joynt, Thomas ST Li, Joey KM Wai, and Florence HY Yap)

Address for correspondence:

Gavin M. Joynt MBBCh, FHKCA(IC), FJFICM
 Department of Anesthesia and Intensive Care
 Chinese University of Hong Kong
 Prince of Wales Hospital
 Shatin, Hong Kong
 Tel: (852) 2632 2735
 Fax: (852) 2637 2422
 Email: gavinmjoynt@cuhk.edu.hk

after the first description of fat in the lungs of a trauma victim by Zenker in 1862 [11]. This paper will review current concepts of the etiology, pathophysiology, diagnosis, prevention and therapy of FES.

Etiology

There is a close relationship between fractures, particularly of the pelvis and long bones of the lower limb and FES. Patients with multiple fractures may have a higher incidence of FES [12]. Fat embolism frequently results from marrow intravasation caused by the high intramedullary pressures generated during reaming and the application of cement during arthroplasty, although the incidence of FES is much lower [13]. The trigger for the development of FES in some of these patients is not known. Non-traumatic fat embolism syndrome is also known to occur, but is rare and the origin of fat in these circumstances may be metabolic. A list of previously described etiologic factors and possible mechanisms in the development of FES is shown in **Table 1**.

Pathophysiology

The pathophysiology of FES remains controversial. Fat micro emboli are frequently present within the pulmonary and systemic vasculature following fractures but the amount of microvascular fat appears unrelated to the severity of clinical findings and it is clear that not all patients with fat emboli develop fat embolism syndrome. The development of FES appears to require three factors: a source of circulating fat, embolization of fat globules to pulmonary capillaries and the “activation” of the fat to develop fat embolism syndrome [10].

The fat droplets may be generated by various mechanisms. The mechanical theory states that fat and marrow contents enter the venous system through ruptured medullary venous sinuses after an event such as a bone fracture [14]. Fracture hematoma, excess movement, reaming or the introduction of

prosthetic cement under pressure may increase intra-medullary pressure and facilitate the entry of fat into the circulation [13,15]. Experimental and clinical evidence supporting the mechanical theory of causation includes the histological confirmation of bone marrow contents in embolized fat, the presence of marrow fat in the ipsilateral femoral vein during fracture reduction and reaming and evidence that pressure to the fracture site increases intravasation [15,16]. Fat in the circulation will then lodge in the lung capillaries, causing obstruction to blood flow, and right heart failure. The increase in right heart may lead to an opening of the foramen ovale, possibly explaining the systemic features of the syndrome. The mechanical theory appears incomplete. While up to 95% of skeletal trauma victims have been shown have intravascular fat identified at autopsy and a similar percentage have echocardiographically identified embolism during arthroplasty, the incidence of FES is at most 10%. Systemic effects can occur even in the absence of a patent foramen ovale, and the usual delay of 12 to 72h in presentation of the syndrome is not adequately explained. It is therefore likely that an additional factor may be required to fully explain the pathological and clinical features FES.

A biochemical theory of fat droplet production was originally proposed by Lehman and Moore in 1927 [17]. This theory proposes that there are physicochemical alterations of lipids normally present in the circulation, which result in intravascular fat globule coalition. It is known that acute phase mediators such as C-reactive protein may affect lipid solubility, resulting in agglutination of chylomicrons (1µm in diameter) into larger particles (10-40 µm). These fat globules may then be trapped in pulmonary and other tissue capillary beds. This biochemical theory may explain the occurrence of non-traumatic fat embolism syndrome.

While the above theories adequately explain the presence of fat or marrow particles in the lungs and other tissues, the FES itself is more completely understood by considering the potential toxic nature of the embolized fat particles. The free fatty acids that are released by hydrolysis from circulating lipids at the time of trauma, or during the breakdown of fat in the

lung, are directly toxic to pneumocytes, and vascular endothelium [18]. Once the inflammatory cascade is initiated, release of inflammatory mediators will enhance adherence of platelets and fibrin to emboli, neutral fat hydrolysis further endothelial damage ultimately resulting in acute lung injury or ARDS. Recent observations have concluded that phospholipase A₂, free radicals and pro-inflammatory cytokines are involved in the pathogenesis of ARDS associated with FES [19,20]. The need for the production of sufficient amounts of toxic intermediaries to produce the clinical features of FES may explain the substantial delay usually seen from the time of embolization to the onset of signs and symptoms. Emboli in the cerebral, skin, retinal, renal and other systemic capillaries may result from particles passing directly to the systemic circulation, possibly through a patent foramen ovale or directly through the lung. Other mechanisms such as the activation of the clotting cascade by thromboplastic activity of fat resulting in DIC may contribute to the pathophysiology of fat embolism syndrome.

While one or a combination of the above mechanisms provides a plausible explanation for the pathogenesis of FES, the evidence supporting them is not robust.

Diagnosis

Any patient with long bone or pelvic fractures should be considered at risk of FES. Fat embolism syndrome classically presents with respiratory failure, neurologic dysfunction and a petechial rash [21,22]. Initial manifestations usually occur 24-72h after bone trauma, but in severe cases onset may be more rapid.

Respiratory failure is initially manifested by the onset of hypoxia, which may initially be relatively mild and easily missed if arterial oxygen saturation is not monitored [23]. In some cases hypoxia may progress and when severe is associated with radiological findings of bilateral alveolar pulmonary infiltrates (**Figure 1**). Severe hypoxia usually indicates the onset of acute respiratory syndrome (ARDS).

Neurologic dysfunction often develops after respiratory

failure, but does not respond to improvements in arterial oxygenation. Neurological manifestations consist of confusion, decreased levels of consciousness and rarely seizures or focal deficits. If sought neurological manifestations occur in 50-80% of patients [24]. Non-contrast CT scan may demonstrate patchy lucency over the cerebral cortex [25]. Brain death has been described as a consequence of FES [26].

The petechial rash is found over the upper thorax, axillae and face, but have only a limited distribution. Sometimes conjunctival petechiae may be the most obvious manifestation of the rash (**Figure 2**). Although petechiae in the appropriate clinical setting are highly suggestive of FES, they only occur in a minority (30-50%) of cases and their appearance may be delayed beyond two to three days [9,21,22].

To establish some diagnostic uniformity criteria for the diagnosis of FES have been proposed. The diagnostic criteria suggested by Gurd and Wilson [27] (**Table 2**) and Lindeque *et al* [28] (**Table 3**) are most commonly used, either directly or in a modified form. However, while Gurd and Wilson's criteria are more specific, Lindeque *et al*'s criteria are more sensitive. In particular, the same cohort of high risk patients were found to have rates of positive diagnosis for FES of 13% using Gurd and Wilson's criteria, but 29% using the criteria of Lindeque *et al* [28]. Currently, published literature is difficult to compare because of the widely different criteria used for defining the syndrome. For the same reason the reported incidence of fat embolism syndrome varies widely. Unfortunately the use of laboratory tests such as serum lipase, blood lipids, cytologic examination of urine, sputum or blood and tests on pulmonary artery blood such as the cryostat test have not improved diagnostic ability [29]. Techniques such as pulmonary aspiration, broncho-alveolar lavage and pulmonary microvascular cytology have been used in an attempt to improve diagnostic capability but have limited utility [30,31].

There are several minor manifestations of FES. These include retinopathy, often referred to as Purtscher's retinopathy [32]. Purtscher's retinopathy consists of cotton wool spots, and hemorrhages, often surrounding

the optic disc. They may be associated with visual defects. Lipuria has been described as an occasional finding. Other non-specific findings may include fever, changes in complement levels and coagulation abnormalities.

A fulminant form of fat embolism syndrome occurs rarely, develops in minutes to hours, is associated with profound hypoxemia, hypotension and carries a high mortality [33]. The differential diagnosis of fat embolism syndrome includes pulmonary thromboembolism, pulmonary contusion, fluid overload, intracranial injury, aspiration pneumonitis and ARDS associated with systemic inflammation or sepsis.

Prevention of fat embolism syndrome in high-risk patients

Surgical and medical measures to prevent the development of FES have been investigated. Surgical measures have focused on the timing of fracture immobilization and fixation, as well as fixation methods in trauma. In the case of arthroplasty, methods of reaming, decompression of the marrow cavity and cement strategies have received attention. Several medical therapies have been investigated.

Surgical methods

Both retrospective [34,35] and prospective [36] studies have demonstrated that early fixation of fractures results in a decreased incidence of FES when compared with delayed fixation. The overall rate of pulmonary and septic complications is also reduced [34,36]. Pelvic fractures are best managed by external fixation. Some controversy, however, exists as to the best method of fixation of long bones with authors variably recommending external fixation, internal fixation with reaming and unreamed intramedullary nailing [37]. Intramedullary reaming creates a more stable reduction than unreamed nailing, allowing earlier weight bearing and improved fracture union.

Disadvantages are that the reaming process increases intramedullary pressure and therefore the risk of fat embolism syndrome. The use of unreamed nails may reduce intramedullary pressures and decrease the risk of pulmonary injury [38], and animal studies suggest that nailing techniques may improve the quality of fixation and reduce the incidence of pulmonary complications [39]. There is no clear consensus regarding the best method of fixation.

There is some evidence that internal fixation, particularly with reaming, may worsen established pulmonary injury or FES and that fixation should be delayed in this setting [38], however the appropriate timing of fixation of fractures under these circumstances remains uncertain.

Several methods to prevent FES during total hip or knee arthroplasty have been investigated. Most have focused on reducing intramedullary pressure during the reaming and cementing process [40]. Methods have included drilling a venting hole prior to femoral reaming during hip arthroplasty, and then the use of a distal intramedullary plug prior to cementing the femoral component in place, to prevent pressure transmission to the remaining marrow cavity [15]. Venting and drainage along the linea aspera prior to femoral reaming for hip arthroplasty has been shown to attenuate pulmonary shunt values and echocardiographic evidence of embolization [41]. Similar results were noted during hip arthroplasty when conventional cementing techniques were compared with avoided of cement or cement applied with a novel vacuum technique [42]. The use of a reaming system coupled with a rinsing aspirator, has been shown to have some value in reducing the systemic effects of embolization in animals [43,44]. Placement of a tourniquet on the involved limb reduces emboli only until released and sudden death from massive fat and thromboembolism has been reported following the release of the tourniquet [33].

Medical methods

The features of FES normally develop after an interval

of 12-72h suggesting that there may be a window of opportunity to attenuate or prevent the syndrome with an appropriate pharmacological agent. Several specific pharmacological therapies have been investigated but appear to provide little benefit. Agents have targeted the enhancement or modulation of microvascular flow, fat or fatty acid metabolism, the inflammatory cascade and the coagulation system. In particular, the prophylactic uses of low molecular weight dextran, hypertonic glucose, ethanol, heparin and aspirin have not been demonstrated to be of benefit.

Corticosteroids at different doses have been used to reduce the incidence and severity of hypoxemia and fat embolism syndrome in patients at high risk. The mechanism by which corticosteroids may reduce the incidence of FES is unknown, but could plausibly be related to modulation of the inflammatory reaction associated with the condition. Several prospective studies have assessed the use of corticosteroids as a prophylactic agent in FES. All have assessed the drug methylprednisolone, but at widely varying doses, from 90 mg/kg over four days [45] to 5 mg/kg over 2 days in the most recent study [46]. All prospective randomized studies have demonstrated a reduction in the incidence of FES and hypoxia in the treatment group [28,45-49]. A recent meta-analysis suggested that the pooled relative risk for developing fat embolism syndrome was 0.16 (95% CI: 0.08-0.35) in the methylprednisolone group compared with the control group, and the corresponding relative risk for developing hypoxemia was 0.34 (95% CI: 0.19-0.59) [50]. While these numbers appear impressive, they should be interpreted with great caution. No meaningful hospital or 28 day mortality data was reported in any of the studies. The infection rate in most studies was poorly documented, however when it was, the rate of infection appears higher in the methylprednisolone groups. Subject entry criteria were poorly documented and appear highly variable. Randomization processes, when documented were unsatisfactory and blinding poor. At best, the authors consider the data suggests that methylprednisolone may possibly be a useful prophylactic agent in high-risk patients. Further high quality studies are required before the routine use of methylprednisolone for prophylaxis of FES can be

recommended.

Therapy

There have been no major trials of specific therapeutic regimes for established FES [51]. Initial experimental investigations and human observations have suggested the possible therapeutic utility of several agents. Ethanol is a known lipase inhibitor and emulsifying agent. It was reported that intoxicated trauma victims had a lower incidence of fat embolism syndrome than patients with no recent intake of alcohol [52], but this association has not been confirmed and its clinical use is not currently recommended. The protease inhibitor, aprotinin, was reported to be effective in decreasing mortality in a retrospective study [53]. This observation has not been repeated in a prospective clinical trial and its efficacy is not certain. Recommendations for the use of corticosteroids have traditionally followed those for ARDS, and currently there is insufficient evidence to recommend their use in FES. No significant clinical benefit has been demonstrated in studies investigating the potential benefit of heparin, dextran, aspirin, albumin or glucose loading [54]. A recent controlled animal study suggested that N-acetylcysteine may be useful in attenuating lung injury induced by fat embolism [55].

The natural history of FES is that it is a self-limiting condition that runs its course over about 3-7 days, depending on the severity of the initial insult and currently therapy remains supportive. The usual approach to assessment and urgent treatment of the airway, breathing and circulation is mandatory and the maintenance of adequate oxygenation is the cornerstone of therapy. A decreased level of consciousness and inability to protect the airway may necessitate intubation. Frequent assessment of oxygenation is required and if necessary oxygen is provided by face mask, CPAP, non-invasive ventilation, or intubation and ventilation with PEEP. Current recommendations suggest that following ARDS-net type protocol is reasonable in severe cases [56,57]. Mechanical ventilation should be instituted if arterial oxygen saturation cannot be maintained above 90% or

if there is evidence of respiratory distress, hypercarbia, or exhaustion.

Circulating volume must be maintained, as untreated shock is associated with a poor prognosis in fat embolism syndrome. The best choice of resuscitation fluid for intravascular volume expansion is unknown. It has been suggested that albumin solutions may be beneficial, as albumin is known to bind free fatty acids that may be responsible for much of the tissue inflammation and injury seen in FES [54,58]. Cautious fluid restriction and diuretics may reduce lung water. Central venous pressure monitoring or pulmonary artery catheters aided assessment of fluid status and should be used as clinically indicated. Acute cor-pulmonale may be a complication of severe hypoxia and is managed with fluids, inotropes such as dobutamine and occasionally pulmonary vasodilators.

The condition of FES appears self-limiting and with good organ support outcome should be good. Accurate assessment of outcome is difficult because of uncertain diagnostic criteria, a broad spectrum of disease and the association with conditions that may produce similar systemic inflammatory syndromes such as multiple trauma, burns or pancreatitis. Earlier literature suggested an overall mortality ranging from 10-20%; however in the 1990s the incidence in a specialized trauma center has been reported to be 11% [3]. It is likely that the incidence is currently much lower. Survivors usually have an excellent long-term prognosis although in rare cases long-term renal dysfunction, cerebral hemorrhagic or ischemic

complications (leading to permanent cerebral dysfunction) and permanent cardiac conducting system insults have been described.

Conclusion

Fat embolism syndrome is most commonly diagnosed following traumatic and operative long bone injury. Because no definitive consensus on diagnostic criteria exist, the accurate assessment of incidence, comparative research and outcome assessment is difficult. A reasonable estimate of incidence in patients after long bone or pelvic fractures appears to be about 3-5%. Mortality rates are reported to be around 10%, but may be lower. The FES therefore remains an important cause of morbidity and mortality and warrants further investigation and research to allow proper recognition and development of preventive and therapeutic strategies. Early fracture fixation is likely to reduce the incidence of fat embolism syndrome and pulmonary complications. The best fixation technique remains controversial. The use of prophylactic corticosteroids may be considered to reduce the incidence of FES and in selected high-risk trauma patients but effects on outcome are not proved. New reaming and venting techniques have potential to reduce the incidence of FES during arthroplasty. Unfortunately, no specific therapies are yet proven to be of benefit in FES and treatment remains supportive with priority being given to the maintenance of adequate oxygenation.

Table 1. ETIOLOGIC FACTORS AND POSSIBLE MECHANISMS DESCRIBED FOR FAT EMBOLISM SYNDROME

Etiologic factors	Possible mechanism
Traumatic	
Fractures	Entry of bone marrow contents into damaged medullary vessels
Intramedullary nailing Total hip or knee arthroplasty	Elevated intramedullary pressure, damage to medullary vessels
Liposuction	Entry of subcutaneous fat into disrupted vessels
Non-traumatic	
Intraosseous fluid administration	Entry of fat droplets into medullary vessels and then the general circulation
Sickle cell disease	Bone marrow necrosis, entry of fat into disrupted vessels
Acute pancreatitis Long-term steroid administration	Altered physical state of blood lipids or release of FFAs into the general circulation

Table 2. GURD AND WILSON'S DIAGNOSTIC CRITERIA

Major 1: Petechial rash
2: Respiratory symptoms, signs, radiographic changes
3: Cerebral signs unrelated to head injury or other conditions

Minor 1: Tachycardia
2: Pyrexia
3: Retinal changes (fat or petechiae)
4: Renal changes
5: Jaundice

1: Acute fall in hemoglobin
2: Sudden thrombocytopenia
3: High erythrocyte sedimentation rate
4: Fat macroglobulinaemia (>8 μm)

Legend: 1 major, 4 minor criteria and fat macroglobulinaemia are required for diagnosis.

Table 3. CLINICAL CRITERIA PROPOSED BY LINDEQUE *ET AL* FOR DIAGNOSIS OF FAT EMBOLISM SYNDROME AFTER LONG BONE FRACTURES

$\text{PaO}_2 < 60$ mmHg in room air
 $\text{PaCO}_2 > 55$ mmHg or $\text{pHa} < 7.3$
Spontaneous respiratory rate > 35 breaths/min (even after adequate sedation)
Clinical signs of increased work of breathing (dyspnea, accessory muscle use) and tachycardia

Legend: The presence of at least one of these findings in a patient with long bone fracture(s) establishes the diagnosis of fat embolism syndrome.

Figure 1. TYPICAL BILATERAL PULMONARY INFILTRATES IN A PATIENT WITH ALL THE FEATURES OF CLASSICAL FAT EMBOLISM SYNDROME, INCLUDING SUB-CONJUNCTIVAL PETECHIAE AND A SEVERE CONFUSIONAL STATE

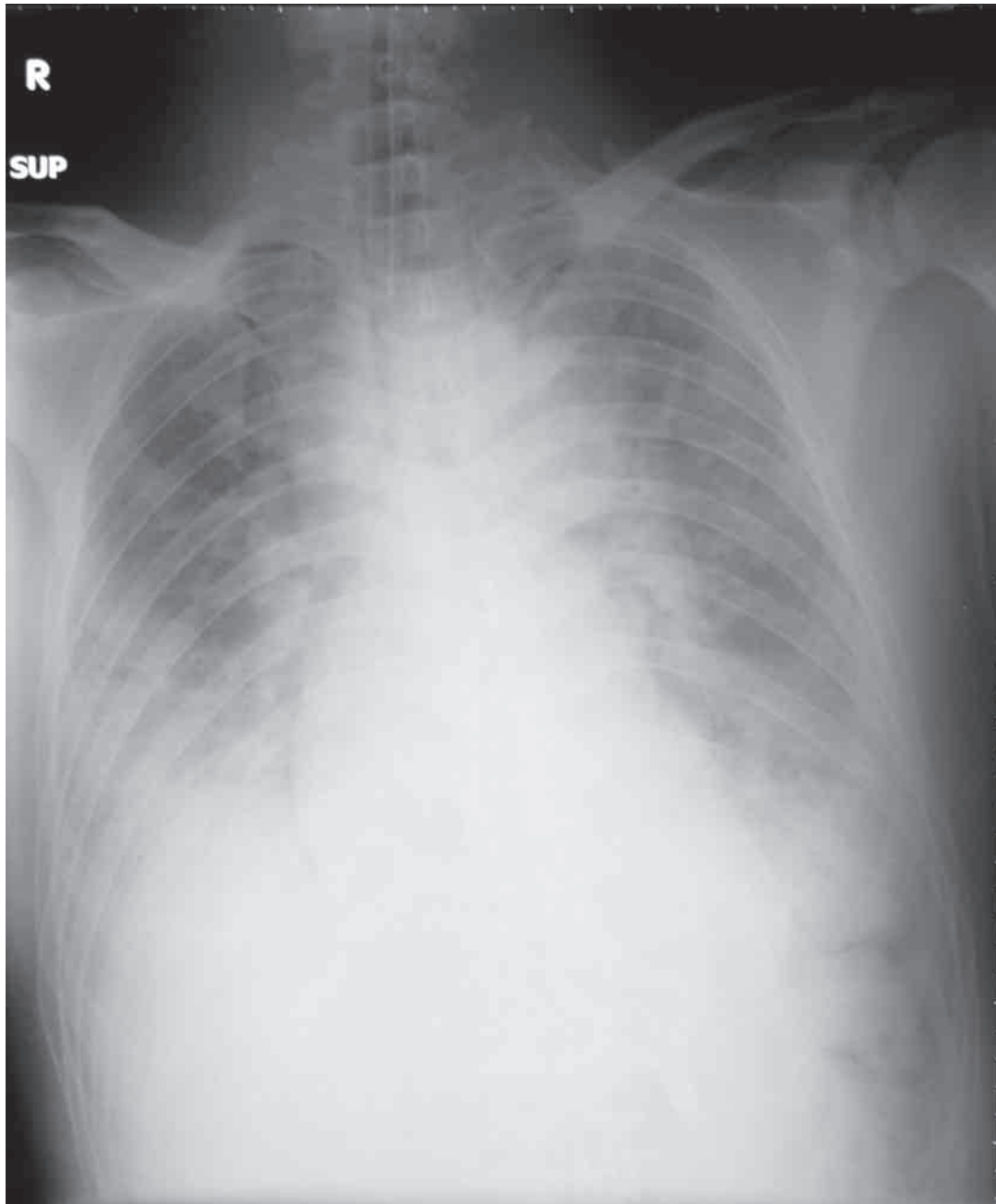


Figure 2. SUB-CONJUNCTIVAL PETECHIAE IN THE SAME PATIENT WHO DEMONSTRATED ALL THE FEATURES OF CLASSICAL FAT EMBOLISM SYNDROME



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